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SYSTEMATIC REVIEW AND META-ANALYSIS

Vitamin D Deficiency and the Risk and Severity of Chemotherapy-Induced Peripheral Neuropathy in Adults with Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy is the commonest neurological complication of cancer treatment and has no established preventive therapy. Vitamin D deficiency is a plausible, cheaply correctable risk factor, but the only previous pooled estimate rested on two studies.

Objective: To estimate the association between vitamin D deficiency or insufficiency and the risk and severity of chemotherapy-induced peripheral neuropathy, and to determine how much of the between-study variation is attributable to how neuropathy was ascertained.

Methods: PubMed/MEDLINE and Europe PMC were screened, with four further sources and citation tracking. Cohort, cross-sectional and trial-embedded studies reporting serum 25-hydroxyvitamin D against neuropathy in adults were eligible. ROBINS-E was used. Random-effects models pooled odds ratios and, separately, Hedges g for 25-hydroxyvitamin D concentration. Ascertainment method was a pre-specified moderator.

Results: Fourteen studies (3,654 participants) were included, seven poolable (2,118). The unstratified pooled odds ratio was 3.45 (95% confidence interval 1.97 to 6.03), I^2 74.6%. Ascertainment explained 93.5% of between-study variance: patient-reported instruments gave 5.27 (3.41 to 8.13, I^2 0%) and clinician-graded NCI-CTCAE gave 1.72 (1.29 to 2.29, I^2 8.0%); ratio of odds ratios 3.01 (1.69 to 5.35). 25-Hydroxyvitamin D was lower in affected patients (g 0.58, 0.28 to 0.88). Bias-adjusted estimates ranged from 1.44 to 2.40. Certainty was very low, rising to low for the clinician-graded estimate.

Conclusion: Vitamin D deficiency was associated with chemotherapy-induced peripheral neuropathy, but the magnitude depended almost entirely on how neuropathy was measured. The defensible estimate is a 1.7- to 2.4-fold increase in odds, not threefold.

1. Introduction

Chemotherapy-induced peripheral neuropathy is the commonest neurological complication of systemic cancer treatment and, for many survivors, the one that outlasts the disease. In a multicentre prospective registry of patients receiving oxaliplatin- or taxane-based regimens, sensory neuropathy of grade 2 or worse developed in 44.4% within twelve months, and more than seven in ten of those cases had appeared within ninety days of starting treatment.[1] Among 2,135 patients with gastro-oesophageal cancer followed for two years, neuropathy scores rose sharply during chemotherapy and never returned to baseline, tracking a persistent decrement in health-related quality of life.[2] In a population-based cohort of early breast cancer survivors assessed a median of 3.6 years after taxane treatment, sensory symptoms persisted in up to 48.4% and motor symptoms in up to 61.3%.[3] Five years after oxaliplatin, motor neuropathy scores showed no decline with elapsed time and remained associated with worse quality of life and greater psychological distress.[4]

What is being counted here is a specific and recognisable disorder of nerve, and it is worth stating the phenotype before the arithmetic. Taxane- and platinum-induced neuropathy is characteristically a length-dependent, sensory-predominant, symmetrical axonal polyneuropathy that begins in the toes and ascends in a stocking-and-glove distribution. Taxanes injure both small and large fibres, so that loss of vibration sense and proprioception, depressed or absent ankle reflexes and, in severe cases, sensory ataxia accompany the more familiar numbness, tingling and burning; motor and autonomic involvement occur but are rarely dominant. Oxaliplatin produces two syndromes that should not be conflated: an acute, cold-triggered channelopathy with perioral and

pharyngolaryngeal paraesthesiae appearing within hours of infusion, and a chronic cumulative sensory neuropathy resembling the taxane picture. Bortezomib and thalidomide, used in multiple myeloma, produce a predominantly small-fibre, painful sensory neuropathy. One feature common to all of them bears directly on when the outcome is measured: coasting, in which symptoms continue to worsen for weeks or months after the last dose, so that a study assessing neuropathy only at the end of treatment will systematically undercount it relative to one that follows patients afterwards.

The consequences reach beyond symptom burden. Neurotoxicity is among the commonest reasons for interrupting or abandoning curative-intent chemotherapy. Among older adults receiving oxaliplatin, neuropathy raised the rate of intercycle delay by 87% and more than doubled the risk of early discontinuation.[5] In women treated for non-metastatic breast cancer, receipt of a taxane independently predicted dose delay, dose reduction and early discontinuation, with toxicity the commonest stated reason.[6] A neurological complication therefore becomes an oncological one, because the dose a patient does not receive is the dose that does not treat the tumour.

Against this burden stands a conspicuous therapeutic vacuum. Randomised trials of hand cooling and compression have reduced grade 2 or worse sensory neuropathy in the treated hand,[7] and sensorimotor training and whole-body vibration have lowered neuropathy incidence from 70.6% to 30.0% and 41.2% respectively,[8] but these are physical interventions of limited reach, and pharmacological prevention remains unsettled: a double-blind trial of duloxetine reduced new-onset neuropathy yet left paraesthesia, numbness and cold sensitivity unchanged.[9] No agent has entered routine practice. Prevention has therefore turned towards modifiable host factors, and several have been identified — lower pre-treatment haemoglobin, higher body mass index and older age,[10] obesity and larger body surface area,[11] diabetes and other comorbidity,[12] African American ancestry,[13] and variation in CYP2C8.[14] Of these, almost none can be altered before chemotherapy begins.

Vitamin D is the striking exception, because it is measurable in a routine laboratory, correctable within weeks and inexpensive. The proposed biology is specific to peripheral nerve rather than generic. The vitamin D receptor and the activating enzyme 1-alpha-hydroxylase are both expressed in dorsal root ganglion neurones and in Schwann cells, so the ganglion can generate and respond to the active metabolite locally. Calcitriol induces neurotrophic factors, among them nerve growth factor and glial cell line-derived neurotrophic factor, that support small-fibre survival and axonal maintenance. It restrains pro-inflammatory cytokine release from macrophages resident within the dorsal root ganglion, which matters here because taxane and proteasome-inhibitor neurotoxicity both involve ganglionic neuroinflammation rather than a purely direct axonal insult. Vitamin D signalling also influences axonal regeneration and remyelination after nerve injury, and modulates calcium handling in a manner relevant to nociceptor excitability. It should be said plainly that most of this rests on animal and laboratory work rather than on human nerve, and that a wholly different explanation is available and cannot be excluded by any study in this review: patients who are unwell, immobile, indoors and cachectic have lower 25-hydroxyvitamin D, so deficiency may mark frailty and poor nutritional reserve rather than cause nerve injury. The human observational data are nevertheless consistent. In 3,629 inpatients with type 2 diabetes phenotyped by nerve conduction study, vitamin D deficiency was independently associated with subclinical distal symmetrical polyneuropathy (odds ratio 1.65, 95% confidence interval 1.31 to 2.08).[15] In elderly patients assessed by electromyography and skin conductance, deficiency was an independent risk factor for neuropathy and acted predominantly through large-fibre injury.[16] A multicentre study found the relationship non-linear, with neuropathy severity accelerating below approximately 26 ng/mL.[17] In a case-control study using skin-biopsy intraepidermal nerve fibre density, 25-hydroxyvitamin D was lower in small-fibre neuropathy than in controls.[18] Peripheral blood mononuclear cells from patients with diabetic neuropathy showed reduced vitamin D receptor and Sirtuin 1 expression, both correlating with autonomic reflex testing.[19] The exposure is also common where it matters. In Minangkabau women in West Sumatra, 73% were vitamin D deficient or insufficient despite an equatorial setting;[20] in an Indonesian breast cancer cohort every patient assessed was deficient, with a median 25-hydroxyvitamin D of 8.94 ng/mL;[21] in urban Sri Lanka 93.9% of adults had low vitamin D;[22] severe deficiency affected 71% of urban adults in the National Capital Region of Delhi;[23] and half of Thai patients with advanced colorectal cancer were deficient.[24] Tropical latitude does not protect.

Yet the evidence linking vitamin D status to chemotherapy-induced peripheral neuropathy has never been synthesised in its own right. A scoping review mapped eleven observational studies narratively but, by design, produced no pooled estimate, no heterogeneity statistic and no assessment of bias.[25] The single published pooled estimate appeared as one line among sixteen candidate influencing factors in a broader meta-analysis and rested on only two contributing studies.[26] An estimate built from two studies cannot support subgroup analysis, cannot be tested for small-study effects and cannot yield a prediction interval. Meanwhile the analogous question in diabetes has been answered: a meta-analysis of randomised trials in painful diabetic neuropathy pooled four trials and found a standardised mean difference of −0.85 (95% confidence interval −1.07 to −0.62) favouring vitamin D.[27] The cancer analogue remains untested.

A second problem has gone unexamined. Chemotherapy-induced peripheral neuropathy is

captured in two fundamentally different ways — by a clinician assigning a Common Terminology Criteria for Adverse Events grade, or by the patient completing a validated instrument — and these two routes do not agree. In the phase III PANTHER trial, clinician grades were consistently lower than patient-reported severity, with weighted kappa between 0.07 and 0.34 across six symptom domains.[28] In phase I trials, nineteen clinician-reported items were recorded at 1% or less while the matched patient-reported items were reported at 10% or more.[29] In routine outpatient chemotherapy, including for peripheral neuropathy specifically, patient-clinician agreement was only fair to moderate.[30] In the phase III POLARIX trial patients consistently reported a higher incidence of symptoms than clinicians.[31] Among 1,033 participants undergoing 1,623 neurotoxicity assessments, patient-reported measures outperformed clinician and neurophysiological tools on convergent validity and responsiveness.[32] If the measuring instrument changes the observed frequency of the outcome, it may also change the observed size of any association with an exposure — and no synthesis in this field has tested that.

The novelty of this study lies in four things. It is the first dedicated quantitative synthesis of this question, assembling every extractable contrast between vitamin D status and chemotherapy-induced peripheral neuropathy and pooling seven studies against the two behind the only previously published estimate. It tests outcome ascertainment, assay method, exposure threshold, tumour type and risk of bias as formal moderators, rather than describing heterogeneity and leaving it unexplained. It runs a second analysis on the serum 25-hydroxyvitamin D concentration itself, so that the conclusion does not rest on a single effect measure. And it applies an internal-consistency audit that checks each primary study against its own reported discrimination, a rarely used test that here identified one influential study whose numbers cannot all be true. The aim of this study was to estimate the association between vitamin D deficiency or insufficiency and the risk and severity of chemotherapy-induced peripheral neuropathy in adults receiving neurotoxic chemotherapy, and to determine how much of the variation between studies is attributable to the method by which neuropathy was ascertained.

2. Methods

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[33] It was not prospectively registered.

2.1. Search strategy

Two sources supplied the records that entered formal screening: PubMed/MEDLINE, searched through the National Center for Biotechnology Information E-utilities interface, which returned 161 records, and Europe PMC, including PubMed Central and non-MEDLINE content, which returned 289. Scopus, Web of Science, the Cochrane Library and Google Scholar were separately interrogated for the same concept blocks and returned no eligible primary study that was not already held; they contributed no unique records to the count and are therefore not represented in the flow diagram. No language, geographical or publication-status restriction was applied, although the search terms themselves were in English and no translation workflow was used, which is recorded as a limitation. The Boolean string, given here in PubMed syntax, was: (("vitamin D" OR "cholecalciferol" OR "ergocalciferol" OR "calcifediol" OR "25-hydroxyvitamin D" OR "25(OH)D") AND ("peripheral neuropathy" OR "polyneuropathy" OR "neurotoxicity" OR "neuropathic pain" OR "paraesthesia") AND ("chemotherapy" OR "paclitaxel" OR "nab-paclitaxel" OR "docetaxel" OR "taxane" OR "oxaliplatin" OR "cisplatin" OR "carboplatin" OR "bortezomib" OR "thalidomide" OR "vincristine")). Retrieval was supplemented in three ways. First, the reference list of the only dedicated review of this question was resolved item by item and every one of its eleven included primary studies was checked against the present set.[25] Second, backward citation chasing was performed on eight seed papers, yielding 361 unique works. Third, forward citation chasing was performed on the same seeds. The deduplicated union of the database searches comprised 427 unique records, and neither citation-chasing route produced an additional eligible primary study.

2.2. Eligibility criteria

Studies were eligible if they enrolled adults aged 18 years or over with a confirmed malignancy who were receiving neurotoxic systemic chemotherapy; measured serum 25-hydroxyvitamin D before or during that chemotherapy and reported it either against a stated deficiency or insufficiency threshold or as a continuous variable compared between neuropathy groups; assessed chemotherapy-induced peripheral neuropathy with a named instrument; and reported data sufficient to derive an odds ratio, or an adjusted effect estimate with a confidence interval, or a between-group comparison with a p value. Prospective and retrospective cohorts, cross-sectional studies with comparative data, correlative analyses nested in randomised trials, and prospective interventional studies of vitamin D repletion were all admissible.

Studies were excluded if the exposure was dietary intake, multivitamin use or vitamin D receptor genotype without a serum measurement; if the neuropathy was not attributable to chemotherapy; if the outcome was reported only within a composite quality-of-life score; or if the report was a review, editorial, protocol, conference abstract without a full paper, case report, animal study or laboratory study. Two decisions deserve explicit statement. A correlative analysis of supplement use within the SWOG S0221 cohort was excluded because its exposure was self-reported multivitamin use rather than a serum measurement and because it overlapped a study already included, which would have double-counted participants. A randomised trial of compression and

exercise was excluded because 25-hydroxyvitamin D was a downstream biochemical outcome of that intervention rather than the exposure under study.

2.3. Data extraction

Data were extracted into a structured workbook covering study design, setting, recruitment period, funding and declared conflicts; population, sample size, age, sex, diabetes prevalence and body mass index; chemotherapy agent, dose and schedule; vitamin D assay platform, sampling timing, units, threshold, prevalence below threshold and concentrations by neuropathy status; and the neuropathy instrument, case definition, assessment schedule and incidence. Full texts rather than abstracts were the source wherever a full text existed. Screening, data extraction and risk-of-bias appraisal were carried out by a single reviewer and were not performed in duplicate, so no measure of inter-rater agreement is available and the reconstruction decisions described below were not independently verified. This is a real weakness and is listed among the limitations rather than left for the reader to infer. To offset it as far as possible, the complete extraction workbook, the analysis dataset and the analysis code have been retained and are available from the corresponding author, so that both reconstructed contrasts can be checked by a reader who wishes to do so.

Each two-by-two table was labelled by the strength of its provenance, and this labelling governed how the study was used. A printed table had all four cells given by the authors, or had cases printed and non-cases obtained by subtraction from printed group totals. A derived table was obtained arithmetically from printed percentages. A reconstructed table was recovered by back-solving a reported statistic, such as an operating point on a receiver operating characteristic curve or a published odds ratio against known group totals. No cell count was imputed from an assumed distribution. Distributional assumptions were, however, unavoidable in the continuous strand, where the conversion of medians and interquartile ranges assumes approximate normality, the derivation of an effect size from a p value assumes a t distribution, and the conversion between an area under the curve and a standardised difference assumes binormality with equal variances; each is stated where it is used. Provenance was then carried into the analysis as a moderator and as a restricted pool, so that a reader can see exactly what the weaker data contribute.

Where a source contained mutually contradictory numbers, the contradiction was recorded rather than resolved silently, and the value whose denominators could be verified arithmetically was preferred. Three studies required this. One printed group sizes of 273 and 77 in its text against 277 and 73 in its tables, and only the latter reproduced both the stated incidence and the published odds ratio, so the tabulated values were used.[34] One described its assay as an electrochemiluminescence immunoassay in the methods and as mass spectrometry in the abstract and discussion, printed outcome categories summing to 297 of a stated 300 participants, and gave two different adjusted odds ratios for one model; the methods description and the tabulated estimate were used.[35] One reported 77 neuropathy cases in its results and 71 in its discussion, of which only 77 matched its own printed subgroup counts.[36] Every such decision is stated in the results.

2.4. Risk of bias assessment

Risk of bias was appraised with ROBINS-E, the instrument for non-randomised studies of exposure effects, across its seven domains: confounding, exposure measurement, participant selection, post-exposure interventions, missing data, outcome measurement and selective reporting.[37] The overall judgement took the least favourable domain, as the tool specifies. The Cochrane risk-of-bias 2.0 tool was considered and set aside on methodological grounds: every included study is a non-randomised study of an exposure, and even the one study embedded in a randomised trial contributes a comparison between vitamin D strata that was not itself randomised, so a tool built to interrogate randomisation and allocation concealment would have had nothing to appraise. The Newcastle-Ottawa Scale was applied in parallel for comparability with earlier work in this literature. Where the two instruments disagreed, the ROBINS-E judgement governed.

2.5. Statistical analysis

Two analytical strands were run. The first pooled odds ratios for the dichotomous outcome. The second pooled Hedges g for the serum 25-hydroxyvitamin D concentration compared between patients who did and did not develop neuropathy. Running both was deliberate: a standardised mean difference cannot be computed from a two-by-two table because neuropathy is a binary event, but it is the correct measure for the concentration comparison, and an association that survives on two independent effect measures is more trustworthy than one that rests on either alone.

Both strands were fitted with random-effects models. Two estimators were used throughout: DerSimonian-Laird, which is the convention in this literature and permits comparison with earlier work, and restricted maximum likelihood with the Hartung-Knapp adjustment, which is the more appropriate choice when fewer than fifteen studies contribute because DerSimonian-Laird intervals are known to be too narrow in that setting. Both are reported for every pooled estimate for which both were computed, and the Hartung-Knapp result is quoted first when the two differ materially. Where only the DerSimonian-Laird estimate exists, this is stated explicitly rather than left implicit. Heterogeneity was quantified by I^2 with its confidence interval, by τ^2, by Cochran Q, and by a 95% prediction interval. For the continuous strand, three extraction routes were used and compared: direct entry of means and standard deviations, conversion of medians and interquartile ranges by the Wan method, derivation from a reported area under the receiver

operating characteristic curve, and derivation from a p value with group sizes. Areas under the curve, standardised mean differences and log odds ratios were interconverted by the standard identities relating them, and the between-route difference was tested.

Neuropathy ascertainment method — clinician-graded Common Terminology Criteria versus patient-reported instrument — was pre-specified as the primary moderator. Eight further moderators were examined: vitamin D assay platform, exposure threshold, tumour type, study design, provenance of the two-by-two table, geographical region, overall risk of bias, and outcome construct. Two meta-regressions were fitted, on publication year and on the logarithm of sample size. Because k was small, the ascertainment moderator was additionally tested by a permutation procedure with 10,000 permutations, by the Knapp-Hartung small-sample adjustment, after excluding the single influential study, after adjustment for the logarithm of sample size and after adjustment for outcome construct.

Sensitivity analyses comprised leave-one-out omission, Cook distance influence diagnostics, nine restricted pools and four alternative estimators (Mantel-Haenszel, Peto, DerSimonian-Laird, and restricted maximum likelihood with the Hartung-Knapp adjustment). Small-study effects were examined by the Egger regression test, the Begg rank correlation test, trim-and-fill, the precision-effect test, the precision-effect estimate with standard error, and limit meta-analysis; all are reported as exploratory because fewer than ten studies contributed, which is below the threshold at which such tests have useful power. Certainty of evidence was rated with the GRADE approach for three outcomes. Absolute risks and numbers needed to harm were computed against baseline risks taken from the two included studies with genuine cohort sampling. Analyses were performed in R with the metafor, meta and metasens packages; statistical significance was two-sided at 0.05. Three analyses that a reader might reasonably expect were not performed, and are named here rather than left to be discovered. An asymmetry test free of the dependence between the log odds ratio and its variance, such as the Peters or Harbord test, was not computed, so the Egger result is reported with that dependence stated as a caveat rather than corrected. The Hartung-Knapp adjustment was computed for the whole-pool estimates and for the ascertainment moderator, but not for every subgroup and restricted pool, so the intervals in the subgroup and sensitivity tables are DerSimonian-Laird intervals and should be read as the narrower of the two possibilities. A full leave-one-out refit of the moderator meta-regression was not run; a single omission was, and it is reported. No number in this paper has been generated to fill any of these gaps.

3. Results

3.1. Study selection

The two screened sources returned 450 records, 161 from PubMed/MEDLINE and 289 from Europe PMC; the four further sources interrogated returned no eligible primary study not already held. After 23 duplicates were removed, 427 records were screened on title and abstract and 388 were excluded for lacking a chemotherapy-neuropathy concept. All 39 reports sought for retrieval were obtained and assessed in full. Twenty-five were excluded: 17 reviews, editorials or protocols, five with no vitamin D measurement, two non-human studies and one in which the outcome was not chemotherapy-induced neuropathy. Fourteen studies met all eligibility criteria. Seven of these could not contribute to the pooled odds ratio — six because no two-by-two table could be extracted or derived, and one because it was a single-arm interventional study with no comparator, leaving seven studies in the quantitative synthesis. The flow of records, from the 450 identified through to the seven that entered the pooled analysis, is set out in Figure 1.

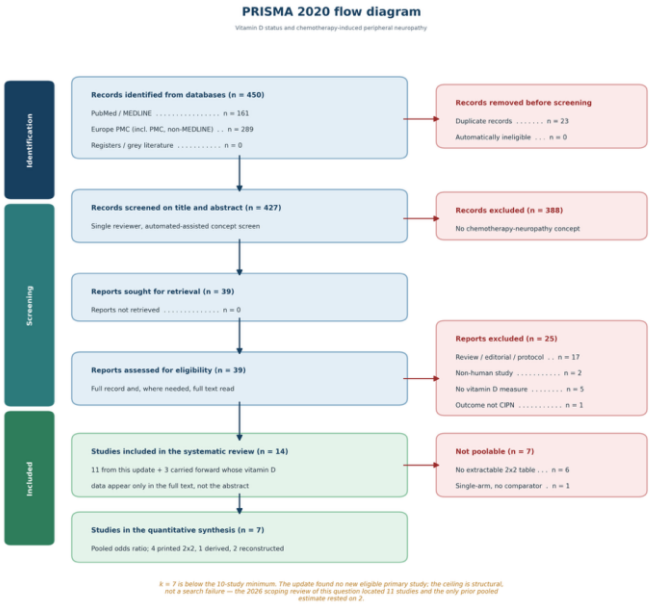

Figure 1. PRISMA 2020 flow diagram showing records identified, screened, assessed for eligibility and included. Fourteen studies met the eligibility criteria and seven contributed to the pooled odds ratio.

3.2. Characteristics of the included studies

The 14 included studies enrolled 3,654 participants across seven countries and three continents. Their designs, populations, chemotherapy regimens, assays, thresholds, instruments and risk-of-bias judgements are set out study by study in Table 1. Five were prospective cohorts, three retrospective cohorts, four cross-sectional, one a correlative analysis nested in a phase III randomised trial and one a prospective single-arm interventional study of vitamin D repletion. Breast cancer treated with a taxane was the commonest setting, contributing seven studies; five concerned multiple myeloma treated with bortezomib or thalidomide, one concerned colorectal cancer treated with oxaliplatin, and one enrolled a cervical or mixed population. Reported neuropathy incidence ranged from 16.0% to 82.8%, a spread that reflects differences in case definition at least as much as differences in true frequency.

Exposure characterisation was markedly uneven. Only one study used liquid chromatography with tandem mass spectrometry, the reference method, and did so with blinded, randomised batch order.[38] Two used a chemiluminescence or electrochemiluminescence immunoassay.[35,39] The remaining eleven did not state an assay platform at all. Deficiency thresholds ranged from 12 ng/mL to 30 ng/mL, one study derived its own threshold from a receiver operating characteristic curve,[39] two treated 25-hydroxyvitamin D as a continuous variable, and two reported a categorical vitamin D variable without printing any numeric threshold, units or assay anywhere in the article.[34,40]

Outcome ascertainment was equally uneven, and one point of self-criticism belongs here. The eligibility criterion required a named instrument, and for nine studies one was named. For three, the source described only a validated questionnaire without naming it; one referred generically to a neuropathy assessment; and one reported membership of a latent class trajectory, which is a method of grouping longitudinal scores rather than an instrument at all. These five were retained because excluding them would have removed most of the myeloma evidence and two of the three largest cohorts, but the criterion was in practice applied more loosely than stated, and readers should know that. One study deserves particular note in a neurological context: it was the only one in the entire set to confirm neuropathy electrophysiologically, by clinical assessment together with nerve conduction studies.[41] That is the most informative ascertainment method available for this outcome, and it is unfortunate that the study reported vitamin D only as a continuous per-unit adjusted odds ratio, so that no two-by-two table could be built and it could not enter the pooled analysis. No included study used skin biopsy, quantitative sensory testing or corneal confocal microscopy.

Table 1. Characteristics of the 14 included studies.

Study	Country	Design	N	Cancer and chemotherapy	Assay; cut-off	Instrument	Case definition	Cases/N (%)	RoB
Grim 2017[39]	Czechia	Prospective cohort	70	Breast (mostly); paclitaxel 80 mg/m^2 weekly × 12	Immunoassay; own cut-off 34 nmol/L	MNSI (patient)	Any grade	42/70 (60.0)	High
Wang 2016[42]	USA	Cross-sectional	111	Myeloma; bortezomib and/or thalidomide	[NR]; <20 ng/mL	CTCAE (clinician)	Grade >2	[NR]	High
Nath 2020[43]	Australia	Retrospective cohort	41	Myeloma; active therapy	[NR]; not reported	Questionnaire (patient)	Any grade	[NR]	High
Jennaro 2020[44]	USA	Prospective cohort	37	Breast I–III; paclitaxel 80 mg/m^2 weekly × 12	[NR]; <20 ng/mL	CIPN20 (patient)	Score; disruption	12/37 (32.4)	Some
Yildirim 2020[45]	Turkey	Retrospective cohort	186	Colorectal; oxaliplatin (FOLFOX)	[NR]; not dichotomised	NCI-CTCAE (clinician)	Grade 2–3	78/186 (41.9)	High
Oortgiesen 2022[46]	Netherlands	Cross-sectional, multi	120	Myeloma; myeloma therapy	[NR]; <75 nmol/L	Questionnaire (patient)	Any grade	83/120 (69.0)	High
Chen 2023[38]	USA (SWOG)	Nested in phase III RCT	1,191	Breast, early; paclitaxel 80 weekly or 175 mg/m^2 2-weekly	Mass spectrometry; ≤20 ng/mL	NCI-CTCAE v3.0 (clinician)	Grade ≥3 sensory	195/1,191 (16.4)	Low
Oortgiesen 2023[47]	Netherlands	Prospective single-arm	39	Myeloma; therapy plus vitamin D repletion	[NR]; <75 nmol/L entry	Questionnaire (patient)	Change in severity	13/35 (37.1)	High
Zhang 2024[36]	China	Cross-sectional	129	Cervical / mixed; paclitaxel 175 mg/m^2 × 6	[NR]; <12 ng/mL	DN4 (patient)	DN4 ≥4	77/129 (59.7)	High
Lixian 2024[34]	China	Prospective cohort	350	Breast; taxane-based	[NR]; not reported	NCI-CTCAE (clinician)	Any grade	277/350 (79.1)	High
Li 2025[40]	China	Cross-sectional, multi	569	Breast survivors; taxane-based	[NR]; categorical	CIPN assessment	Present	471/569 (82.8)	High
Huang 2025[41]	China	Retrospective cohort	161	Myeloma; myeloma therapy	[NR]; not dichotomised	Clinical plus NCS	Present	45/161 (28.0)	High
Xu 2026[48]	China	Prospective longitudinal	350	Breast; chemotherapy	[NR]; categorical	Latent class trajectory	High-risk class	57/350 (16.3)	High
Elfeky 2026[35]	Egypt	Prospective cohort	300	Breast I–III; paclitaxel 80 mg/m^2 weekly × 12 after AC	Immunoassay; ≤20 ng/mL	CIPN20 (patient)	Grade 3–4 sensory	48/300 (16.0)	Some

[NR] = not reported by the source authors. MNSI = Michigan Neuropathy Screening Instrument; DN4 = Douleur Neuropathique en 4 questions; CIPN20 = EORTC QLQ-CIPN20 module; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; AC = doxorubicin and cyclophosphamide; NCS = nerve conduction study; RoB = overall ROBINS-E judgement, in which Some denotes some concerns. Conversion: 1 ng/mL = 2.496 nmol/L. The single-arm repletion study enrolled 39 participants of whom 35 completed the six-month assessment, which is the denominator shown for its outcome. Wang 2016 defined its severity contrast as greater than grade 2, that is grade 3 or worse.

3.3. Risk of bias

Eleven of the 14 studies (79%) were at overall high risk of bias, two raised some concerns and one was at low risk. The domain-level pattern, plotted study by study and summarised by domain in Figure 2, was informative rather than merely discouraging. The two weakest domains were exposure measurement, high in 64% of studies, and confounding, high in 57%. In other words, the dominant threat to this literature is not how neuropathy was counted but how vitamin D was measured and what else was adjusted for. The single low-risk study used mass spectrometry on pre-

treatment samples assayed in blinded, randomised batch order within a pre-specified analysis plan.[38] The Newcastle-Ottawa Scale, applied in parallel, disagreed materially in one case: a study scored 8 of 9 and "Good" on that scale while never reporting its assay, its units or its threshold, an omission the Newcastle-Ottawa instrument has no item to capture.[34] The ROBINS-E judgement of high risk was retained.

Figure 2. Risk of bias across the seven ROBINS-E domains for all 14 included studies, with the Newcastle-Ottawa rating shown alongside for comparison, and the weighted domain summary below. Diamonds mark the seven studies that contributed to the pooled odds ratio.

3.4. Data contributing to the pooled analysis

Seven studies yielded a contrast between vitamin D deficient or insufficient and replete participants. The cell counts, crude odds ratios, provenance and random-effects weight of each are given in Table 2. Four printed the necessary counts or allowed them to be obtained by subtraction from printed totals. One was derived from printed percentages. Two were reconstructed by back-solving a published statistic: one from an operating point on a receiver operating characteristic curve,[39] the other from a published odds ratio against known group totals.[44] Crude odds ratios for individual studies ranged from 1.57 to 8.17 and each was above unity, although the confidence interval included unity in one.[44]

Table 2. The seven contrasts contributing to the pooled odds ratio.

Study	Ascertainment	Outcome	Cases/N deficient	Cases/N replete	Crude odds ratio (95% CI)	2×2 source	Wt (%)	RoB
Grim 2017[39]	Patient-reported	Any grade	34/44	8/26	7.65 (2.57–22.78)	Recon.	12.0	High
Nath 2020[43]	Patient-reported	Any grade	8/11	10/30	5.33 (1.16–24.60)	Derived	8.3	High
Jennaro 2020[44]	Patient-reported	Severe / disruption	7/15	5/22	2.98 (0.72–12.34)	Recon.	9.1	Some
Chen 2023[38]	Clinician NCI-CTCAE	Severe (grade ≥3)	82/397	113/794	1.57 (1.15–2.15)	Printed	20.7	Low
Zhang 2024[36]	Patient-reported	Any grade	59/85	18/44	3.28 (1.54–6.99)	Printed	15.7	High
Lixian 2024[34]	Clinician NCI-CTCAE	Any grade	204/245	73/105	2.18 (1.28–3.72)	Printed	18.4	High
Elfeky 2026[35]	Patient-reported	Severe (grade ≥3)	38/118	10/182	8.17 (3.88–17.22)	Printed	15.9	Some

CI = confidence interval. Weights are from the random-effects model on all seven contrasts. Provenance: printed = all four cells given by the authors or obtained by subtraction from printed totals; derived = obtained from printed percentages; reconstructed (Recon.) = recovered by back-solving a reported statistic.

3.5. Pooled association between vitamin D status and neuropathy

Across all seven contrasts and 2,118 participants, vitamin D deficiency or insufficiency was associated with chemotherapy-induced peripheral neuropathy, with a random-effects pooled odds ratio of 3.45 (95% confidence interval 1.97 to 6.03, $p = 1.4 \times 10^{-5}$) by the DerSimonian-Laird estimator, and 3.42 (1.85 to 6.34, $p = 0.003$) under restricted maximum likelihood with the Hartung-Knapp adjustment, which is the more appropriate inference at this number of studies and is quoted first hereafter. Heterogeneity was substantial: I^2 was 74.6% (95% confidence interval 45.9 to 88.1), τ^2 was 0.367 and Cochran Q was 23.61 on 6 degrees of freedom ($p = 0.0006$). The 95% prediction interval ran from 0.67 to 17.76 and therefore crossed the null. A prediction interval describes where the true underlying effect in a new setting would be expected to lie, and this one is compatible with no association at all. The pooled estimates of both analytical strands, with their heterogeneity statistics and prediction intervals, are given in Table 3.

Restricting the pool to the four studies with printed counts gave 2.92 (1.50 to 5.68), and pooling the three published adjusted odds ratios instead gave 3.86 (1.32 to 11.31). Neither restriction reduced heterogeneity; both left I^2 above 82%.

Table 3. Pooled estimates for both analytical strands.

Analysis	k	n	Pooled estimate (95% CI)	p	I^2 (%)	τ^2
Strand A — pooled odds ratio						
Unstratified pool, all contrasts	7	2,118	3.45 (1.97–6.03)	<0.001	74.6	0.367
Same studies, REML with Hartung-Knapp	7	2,118	3.42 (1.85–6.34)	0.003	74.6	0.332
Printed counts only	4	1,970	2.92 (1.50–5.68)	0.002	82.7	0.370
Published adjusted odds ratios	3	1,841	3.86 (1.32–11.31)	0.014	86.6	0.766
Clinician-graded NCI-CTCAE only	2	1,541	1.72 (1.29–2.29)	<0.001	8.0	0.004
Patient-reported instruments only	5	577	5.27 (3.41–8.13)	<0.001	0.0	0.000
Strand B — pooled Hedges g						
25(OH)D concentration, neuropathy vs none	5	1,876	0.58 (0.28–0.88)	<0.001	79.9	0.088
Same studies, REML with Hartung-Knapp	5	1,876	0.57 (0.22–0.93)	0.011	79.9	0.066
Elfeky entered at its own AUC-implied value	5	1,876	0.42 (0.20–0.64)	<0.001	63.0	0.038

All estimates are DerSimonian-Laird unless the row states restricted maximum likelihood (REML) with the Hartung-Knapp adjustment, which is the preferred inference at this number of studies and is available for the whole-pool rows only. k = number of contributing studies. Strand A pools odds ratios; strand B pools Hedges g for the serum 25(OH)D concentration compared between patients who did and did not develop neuropathy. AUC = area under the receiver operating characteristic curve.

3.6. Outcome ascertainment is the dominant source of heterogeneity

Stratifying by how neuropathy was ascertained removed almost all of the heterogeneity. The two studies that used clinician-graded NCI-CTCAE, which between them contributed 1,541 of the 2,118 participants, gave a pooled odds ratio of 1.72 (1.29 to 2.29) with I^2 of 8.0% and τ^2 of 0.004. The five studies that used a patient-reported instrument, contributing 577 participants, gave 5.27 (3.41 to 8.13) with I^2 of 0.0% and τ^2 of exactly zero. Two cautions are owed here. Heterogeneity was not detectable within either stratum, which at two and five studies with wide individual intervals is not the same as showing that the studies agree; the patient-reported stratum spans point estimates from 2.98 to 8.17, and a τ^2 of exactly zero is a property of the DerSimonian-Laird estimator at small k rather than a property of the data. And the test for subgroup differences, χ^2 17.72 on 1 degree of freedom, is the most anticonservative of the available tests of this contrast; the Knapp-Hartung result reported below is the one that should carry weight. With those caveats, the two strata differed threefold and each was internally consistent. The stratified forest plot, in which both strata, their constituent studies and the overall estimate appear together, is shown in Figure 3.

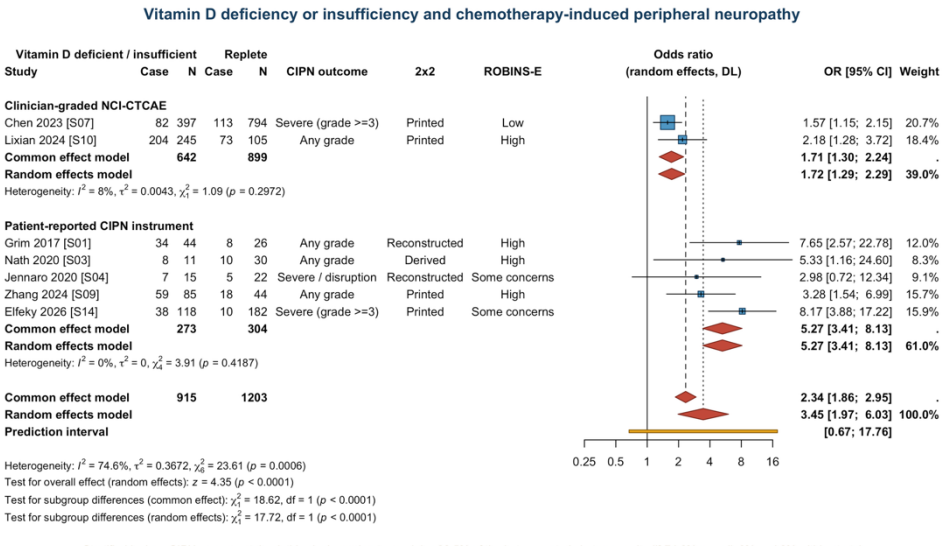

Figure 3. Forest plot of the association between vitamin D deficiency or insufficiency and chemotherapy-induced peripheral neuropathy, stratified by ascertainment method. Squares are individual study estimates, sized by weight; red diamonds are the stratum and overall pooled estimates; the horizontal bar immediately below the overall diamond, labelled Prediction interval, spans 0.67 to 17.76.

Formal meta-regression confirmed the impression from the plot. The ratio of odds ratios for patient-reported versus clinician-graded ascertainment was 3.01 (1.69 to 5.35, Wald p = 0.00018), and this single moderator accounted for 93.5% of the between-study variance, reducing residual I^2 from 74.6% to 13.2%. That proportion is a descriptive quantity from one moderator fitted to seven studies, has no useful sampling distribution and no confidence interval, and should not be read as a precisely estimated parameter. Because k was small the moderator was stress-tested four further ways. The Knapp-Hartung small-sample adjustment, which is the appropriate inference at this number of studies, gave 3.01 (1.50 to 6.03, p = 0.0097); excluding the single influential study gave 2.46 (1.35 to 4.48, p = 0.0032), showing the moderator was not an artefact of that study; and adjusting for outcome construct gave 2.91 (1.41 to 5.98, p = 0.0038), showing

it was not merely the severe-versus-any-grade distinction in disguise. One qualification is important and is stated plainly: adjusting additionally for the logarithm of sample size attenuated the moderator to 3.18 (0.97 to 10.36, p = 0.056), because the two clinician-graded studies were also the two largest. Nor is that the only entanglement. All five patient-reported contrasts are small and three of them rest on derived or reconstructed cell counts, whereas both clinician-graded contrasts are large with printed counts, so ascertainment, sample size and data provenance are three descriptions of very nearly the same partition of these seven studies. The immunoassay subgroup, with two studies and a pooled odds ratio of 8.00, describes the same cluster equally well. At seven studies these explanations cannot be separated, and the moderator should therefore be read as a description of how this literature is organised rather than as an identified causal mechanism. A permutation test was also run, but its result is not quoted here: with seven studies split five against two the smallest attainable permutation p value is one in twenty-one, and a test that can only return its own floor conveys no information. The Knapp-Hartung result and the proportion of variance explained are the evidence that carries weight.

No other moderator accounted for a comparable share of the variance. On meta-regression, assay platform accounted for 38.1% (Wald p = 0.078) and the logarithm of sample size 41.2% (Wald p = 0.102); overall risk of bias, outcome construct, publication year and restriction to breast cancer accounted for none. Two different tests appear in Table 4 and they must not be read interchangeably: the p-between column is a subgroup Cochran Q test computed with stratum-specific between-study variance, whereas the p values quoted in this paragraph are meta-regression Wald tests. The two can disagree, and for assay platform and risk of bias they do. On the subgroup test, tumour type (p = 0.848), study design (p = 0.848), exposure threshold (p = 0.405), provenance of the two-by-two table (p = 0.509) and outcome construct (p = 0.984) were all null.

Three of the subgroup analyses in Table 4 cannot be interpreted independently of one another, and this should be stated rather than left for a reader to discover. The three studies not at high risk of bias are exactly the three studies that used a 20 nanograms per millilitre threshold, so those two rows describe the same partition and return identical numbers. Separately, the four any-grade studies are exactly the four studies at high risk of bias, so those two rows are likewise the same partition. It follows that the earlier statement that adjusting for outcome construct showed the ascertainment moderator was not the severe-versus-any-grade distinction in disguise is weaker than it appears, because in these data outcome construct and risk of bias are one variable. The geographical-region analysis, fitted with five levels across seven studies and three of those levels containing a single study, is saturated and is reported for completeness only; no inference should be drawn from it. All subgroup and meta-regression results are given in Table 4.

Table 4. Subgroup analyses and meta-regressions for the pooled odds ratio.

Moderator	Level	k	Pooled odds ratio (95% CI)	I^2 (%)	p between	R^2 (%)
CIPN ascertainment	Patient-reported	5	5.27 (3.41–8.13)	0.0	<0.001	93.5
	Clinician NCI-CTCAE	2	1.72 (1.29–2.29)	8.0		
25(OH)D assay	Immunoassay	2	8.00 (4.32–14.81)	0.0	<0.001	38.1
	Not reported	4	2.67 (1.78–3.99)	0.0		
	Mass spectrometry	1	1.57 (1.15–2.15)	—		
Geographical region	Europe	1	7.65 (2.57–22.78)	—	<0.001	—
	Oceania	1	5.33 (1.16–24.60)	—		
	North America	2	1.62 (1.19–2.20)	0.0		
	Asia	2	2.50 (1.61–3.86)	0.0		
	Africa	1	8.17 (3.88–17.22)	—		
ROBINS-E overall	High	4	3.41 (1.97–5.91)	37.4	0.004	0.0
	Some concerns	2	5.96 (2.38–14.92)	34.2		
	Low	1	1.57 (1.15–2.15)	—		
Vitamin D threshold	Data-derived (34 nmol/L)	1	7.65 (2.57–22.78)	—	0.405	—
	≤20 ng/mL	3	3.30 (0.98–11.11)	87.7		
	<12 ng/mL	1	3.28 (1.54–6.99)	—		
	Not reported	2	2.53 (1.32–4.86)	14.6		
Tumour type	Breast	5	3.38 (1.67–6.84)	81.4	0.848	0.0
	Multiple myeloma	1	5.33 (1.16–24.60)	—		
	Mixed or uncertain	1	3.28 (1.54–6.99)	—		
Study design	Prospective	5	3.38 (1.67–6.84)	81.4	0.848	—
	Retrospective	1	5.33 (1.16–24.60)	—		
	Cross-sectional	1	3.28 (1.54–6.99)	—		

Moderator	Level	k	Pooled odds ratio (95% CI)	I^2 (%)	p between	R^2 (%)
Provenance of the 2×2 table	Printed	4	2.92 (1.50–5.68)	82.7	0.509	6.7
	Derived	1	5.33 (1.16–24.60)	—		
	Reconstructed	2	5.35 (2.18–13.13)	6.2		
Outcome construct	Any grade	4	3.41 (1.97–5.91)	37.4	0.984	0.0
	Severe (grade ≥3)	2	3.45 (0.69–17.37)	93.7		
	Severe / disruption	1	2.98 (0.72–12.34)	—		
Meta-regression	Publication year (per year)	7	0.96 (0.77–1.19)	78.8	0.686	0.0
	log sample size (per unit)	7	0.72 (0.49–1.04)	51.7	0.083	41.2

The p-between column is a subgroup Cochran Q test computed with stratum-specific between-study variance; the meta-regression rows give Wald p values, and the two tests can disagree. R^2 is the proportion of between-study variance τ^2 accounted for by the moderator, a descriptive quantity at this number of studies. For the meta-regressions the estimate is the ratio of odds ratios per unit of the moderator. Two perfect collinearities exist: the three studies not at high risk of bias are the same three as the ≤20 ng/mL threshold stratum, and the four any-grade studies are the same four as the high risk-of-bias stratum. The geographical-region rows are saturated and not interpretable. Dashes indicate quantities undefined for a single-study stratum. All intervals are DerSimonian-Laird.

3.7. Serum 25-hydroxyvitamin D concentration

Five studies allowed the pre-treatment 25-hydroxyvitamin D concentration itself to be compared between patients who did and did not develop neuropathy, contributing 1,876 participants. Three printed means and standard deviations, or medians and interquartile ranges converted by the Wan method; one gave only an area under the receiver operating characteristic curve with its confidence interval; one gave only a p value with group sizes. Concentrations were lower in patients who developed neuropathy, with a pooled Hedges g of 0.58 (0.28 to 0.88, p < 0.001) and I^2 of 79.9%. The test for a difference between the three extraction routes was null (p = 0.78), which supports the validity of the conversions. Individual study estimates are shown in Figure 4, where the studies are grouped by the route through which their effect size was obtained.

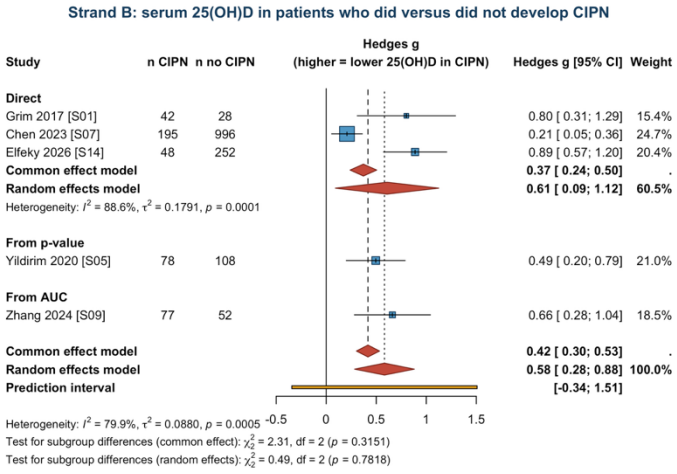

Figure 4. Pooled standardised mean difference (Hedges g) in serum 25-hydroxyvitamin D between patients who did and did not develop chemotherapy-induced peripheral neuropathy, grouped by the route through which the effect size was extracted. The between-route test was null (p = 0.78).

Converting the pooled g to the odds-ratio scale by the standard identity gave an equivalent odds ratio of 2.87. Entering the one internally inconsistent study at its own reported area under the curve rather than at its reported group means gave a pooled g of 0.42 (0.20 to 0.64), equivalent to an odds ratio of 2.14, and dropped I^2 from 79.9% to 63.0%. Both values fall below the unstratified dichotomous pool of 3.45, and the second falls inside the clinician-graded confidence interval.

3.8. Internal-consistency audit

A study that reports both a group difference and a receiver operating characteristic curve has described the same signal twice, and the two descriptions are linked by a fixed mathematical identity. Checking that identity is a strong test of whether a primary study's numbers can all be true at once, and it was applied to every study that reported both. The result of that check, study by study, is given in Table 5. Two studies passed: one reported an area under the curve of 0.730 where its own group difference implied 0.719, and the other reported 0.552 where its group difference implied 0.558.[38,39] One study failed decisively. Its reported group means of 17.5 ± 4.9 against 24.6 ± 8.4 ng/mL imply a standardised difference of 0.89 and therefore an area under the curve of 0.736, yet the same paper reported 0.554 for the same comparison — a 4.7-fold discrepancy in effect size.[35] The same study named 21.5 ng/mL as its optimal threshold with a Youden index of 0.06 while its own primary threshold of 20 ng/mL achieved a Youden index of 0.47; a threshold cannot be optimal while performing eight times worse than a competitor 1.5 units away.

That argument depends on a binormal model with equal variances, and the study in question reported markedly unequal standard deviations, so a sceptical reader might reasonably wonder whether the

incoherence is an artefact of the assumption rather than an error in the source. It is not, and the point can be settled without any distributional assumption at all. For any operating point on an empirical receiver operating characteristic curve, the area under the curve is at least one plus the Youden index J, divided by two, that is AUC ≥ (1 + J)/2. That study's own printed two-by-two table gives a sensitivity of 0.792 and a specificity of 0.683, hence a Youden index of 0.474 and a lower bound on the area under the curve of 0.737. Its reported area of 0.554 is therefore arithmetically impossible against its own table, irrespective of normality, of equality of variances or of skewness. The reverse implication also deserves statement: that reported area of 0.554, converted by the same identities used throughout this review, corresponds to an odds ratio of approximately 1.4, not to the 8.17 that was entered into the pooled analysis. The internal contradiction therefore bears on this study's contribution to the dichotomous strand and not only to the continuous one, which is why the analysis excluding it is reported as a substantive result rather than as a routine check.

The audit also constrains the pooled estimate. An odds ratio of 3.45 corresponds to a standardised difference of 0.68 and hence to an area under the curve of 0.685. The only two studies that actually measured how well 25-hydroxyvitamin D discriminates severe neuropathy obtained 0.552 and 0.554. A pooled association of the size the unstratified model reports sits uneasily with the discrimination the primary studies observed. This comparison should be read as approximate rather than exact. It assumes a continuous, normally distributed marker, whereas six of the seven pooled contrasts dichotomised the exposure at thresholds ranging from 12 to 34 nanograms per millilitre or its equivalent, and the relationship between a dichotomised-exposure odds ratio and the underlying marker's discrimination depends on where the cut falls. There is also an outcome mismatch, since the two measured areas relate to severe neuropathy whereas the pooled odds ratio is dominated by any-grade contrasts. The direction of the discrepancy is nonetheless large enough that it is unlikely to be explained by these assumptions alone.

Table 5. Internal-consistency audit relating each study's reported discrimination to its own reported effect size.

Study	AUC reported	d from its own effect size	AUC implied by that d	d implied by the reported AUC	Ratio	Verdict
Grim 2017[39]	0.730	0.818	0.719	0.867	0.94	Coherent
Chen 2023[38]	0.552	0.208	0.558	0.185	1.12	Coherent
Zhang 2024[36]	0.681	—	—	0.665	—	No group means printed
Elfeky 2026[35]	0.554	0.893	0.736	0.192	4.65	Incoherent
Pooled odds ratio (k = 7)	—	0.683	0.685	—	—	Implies AUC 0.685; the two studies that measured it obtained 0.552 and 0.554

AUC = area under the receiver operating characteristic curve; d = standardised mean difference. The two quantities are linked by the identity $d = \sqrt{2} \times \Phi^{-1}(AUC)$, in which Φ^{-1} is the inverse standard normal distribution function; the identity assumes a binormal model with equal variances. A ratio near unity indicates that a study's own reported numbers are mutually compatible. The assumption-free Youden bound given in the text, AUC ≥ (1 + J)/2, does not depend on that model.

3.9. Sensitivity analyses

The pooled estimate never lost significance on leave-one-out omission, ranging from 2.72 to 4.15, and was essentially unmoved by the choice of estimator: Mantel-Haenszel gave 3.45, Peto 3.40 and restricted maximum likelihood with the Hartung-Knapp adjustment 3.42. One study was formally influential, with a Cook distance of 0.69; omitting it gave 2.72 (1.70 to 4.37) and dropped I^2 from 74.6% to 57.2%.[35] Given the internal contradiction documented above, that omission is a substantive analysis rather than a routine check. Two further results deserve emphasis, and the first requires a correction of emphasis rather than of number. Restricting the pool to the three studies not at high risk of bias gave 3.30 (0.98 to 11.11) with p = 0.054, which is often described as the association failing to survive restriction to the better-conducted studies. That description attributes to study quality what is in fact a two-study contradiction: those three studies include the reconstructed treatment-disruption contrast and the internally inconsistent cohort, and the interval is wide chiefly because two of them disagree with one another, at 1.57 and 8.17, with I^2 of 87.7%. The honest reading is that the three least biased studies do not agree, not that bias was creating the association. And because one study deliberately enriched its analysis cohort for neuropathy cases, its incidence proportions are not population risks and no risk ratio is estimable from it; excluding it, the pooled risk ratio was 2.15 (1.36 to 3.41).[38] The odds ratio is unaffected by that sampling, because outcome-dependent selection preserves the odds ratio. Every sensitivity analysis is tabulated in Table 6, and the leave-one-out results are plotted in Figure 5.

Table 6. Leave-one-out omission, restricted pools and alternative estimators.

Analysis	k	Pooled odds ratio (95% CI)	p	I^2 (%)	Cook d	Infl.?
Omitting Grim 2017	6	3.07 (1.74–5.40)	<0.001	73.5	0.17	No
Omitting Nath 2020	6	3.32 (1.84–6.00)	<0.001	77.7	0.02	No
Omitting Jennaro 2020	6	3.53 (1.92–6.49)	<0.001	78.7	0.01	No
Omitting Chen 2023	6	4.15 (2.45–7.05)	<0.001	51.0	0.43	No
Omitting Zhang 2024	6	3.54 (1.84–6.81)	<0.001	78.0	0.01	No
Omitting Lixian 2024	6	3.93 (1.90–8.13)	<0.001	78.7	0.21	No

Analysis	k	Pooled odds ratio (95% CI)	p	I^2 (%)	Cook d	Infl.?
Omitting Elfeky 2026	6	2.72 (1.70–4.37)	<0.001	57.2	0.69	Yes
Printed counts only	4	2.92 (1.50–5.68)	0.002	82.7	—	
Not at high risk of bias	3	3.30 (0.98–11.11)	0.054	87.7	—	
Patient-reported instruments only	5	5.27 (3.41–8.13)	<0.001	0.0	—	
Clinician-graded NCI-CTCAE only	2	1.72 (1.29–2.29)	<0.001	8.0	—	
Longitudinal designs only	6	3.54 (1.84–6.81)	<0.001	78.0	—	
Breast cancer only	5	3.38 (1.67–6.84)	<0.001	81.4	—	
Cohorts of 100 or more	4	2.92 (1.50–5.68)	0.002	82.7	—	
Mantel-Haenszel estimator	7	3.45 (1.97–6.04)	<0.001	74.7	—	
Peto estimator	7	3.40 (1.99–5.82)	<0.001	74.6	—	
REML with Hartung-Knapp	7	3.42 (1.85–6.34)	0.003	74.6	—	
Risk ratio, excluding the case-enriched cohort	6	2.15 (1.36–3.41)	0.001	83.5	—	

Dashes indicate quantities not applicable to restricted pools. The risk-ratio row excludes the one study whose analysis cohort was deliberately enriched for neuropathy cases, from which no risk ratio is estimable.

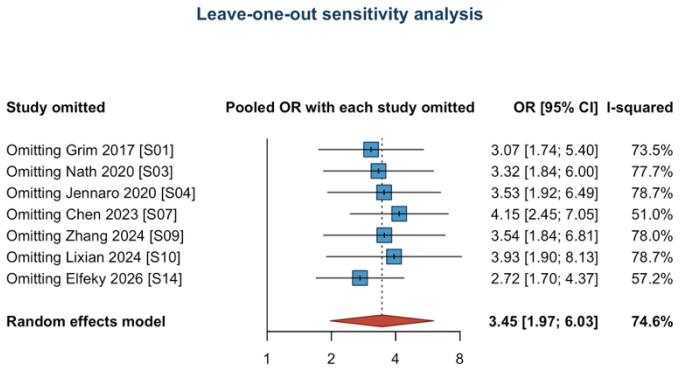

Figure 5. Leave-one-out sensitivity analysis. The pooled odds ratio remained statistically significant with every single study omitted, ranging from 2.72 to 4.15.

3.10. Small-study effects

All small-study-effect analyses are reported as exploratory, because seven contributing studies is below the ten-study threshold at which such tests carry useful power. With that caveat, the pattern was consistent and is set out across six methods in Table 7. The Egger regression test was significant (p = 0.043) while the Begg rank correlation test was not (p = 0.293). The Egger result should be treated with particular reserve, for the mechanical reason set out below; an asymmetry test that does not share that defect, such as the Peters or Harbord test, was not computed, and no substitute figure has been generated in its place. Trim-and-fill imputed four studies and roughly halved the estimate to 1.83 (1.04 to 3.23). The precision-effect test placed the effect at infinite precision at 1.44 (0.60 to 3.47, p = 0.41), a value not distinguishable from no association; because that intercept was not significant at the conventional 0.10 level, the precision-effect test rather than its squared-error variant was taken as the reported estimate, following the standard decision rule. Limit meta-analysis gave 2.40 (1.01 to 5.71). The contour-enhanced funnel plot, carrying the precision-effect regression line and the trim-and-fill imputations, is shown in Figure 6.

One mechanical caveat and one substantive one belong here. Mechanically, the variance of a log odds ratio depends on the estimate itself, so Egger asymmetry is partly built in when effects are large; this is precisely why the ascertainment moderator matters, since it explains the same asymmetry substantively rather than statistically. Two further methods reported here are also operating outside their design conditions: trim-and-fill attributes asymmetry to suppression and was applied to seven studies with I^2 of 74.6%, where much of the asymmetry is heterogeneity-driven, and precision-effect estimation is not a recommended estimator at this number of studies. Their values are reported because they are informative about direction, not because they are dependable as point estimates. Substantively, one asymmetry is invisible in any funnel plot: the single study that explicitly reported no relationship between vitamin D status and the occurrence of neuropathy printed no extractable data and therefore could not enter the pool at all, which biases the pooled estimate upward by an amount no statistical adjustment can recover.[42]

Table 7. Small-study-effect analyses, reported as exploratory because fewer than ten studies contributed.

Test	Stat.	p	Adjusted odds ratio (95% CI)	Note
Egger linear regression	2.69	0.043	—	Exploratory: k = 7 is below the ten-study threshold
Begg rank correlation	1.051	0.293	—	Exploratory
Trim-and-fill	—	0.037	1.83 (1.04–3.23)	Four studies imputed
Precision-effect test (PET) intercept	0.818	0.413	1.44 (0.60–3.47)	Effect at infinite precision; not distinguishable from no association
PEESE intercept	2.57	0.010	2.44 (1.24–4.81)	Regression on the squared standard error
PET-PEESE selected estimate	—	0.413	1.44 (0.60–3.47)	PET intercept p ≥ 0.10, so PET is reported
Limit meta-analysis	—	<0.001	2.40 (1.01–5.71)	Shrinks estimates towards the small-study-adjusted limit

PEESE = precision-effect estimate with standard error; PET = precision-effect test.

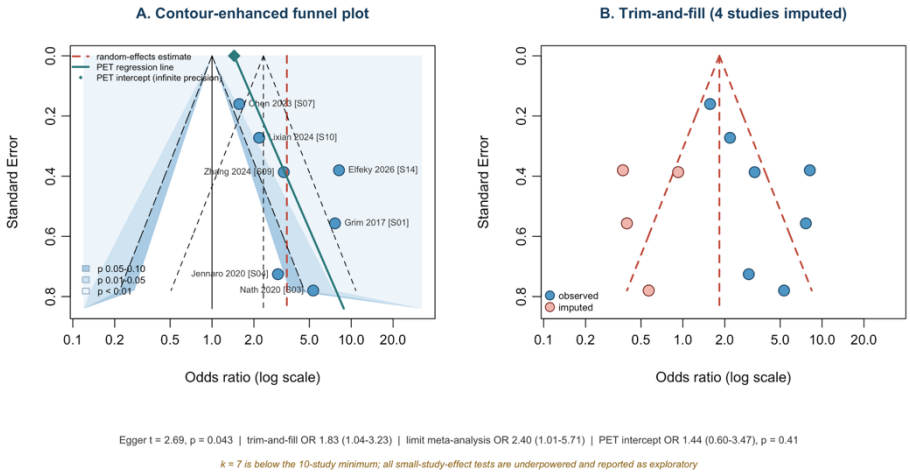

Figure 6. Contour-enhanced funnel plot with the precision-effect test regression line and its intercept, and the trim-and-fill result. No study fell in the non-significant region to the left of the null.

3.11. Convergence of the bias-adjusted estimates

Taken separately, each adjustment above is fragile at this sample size, and they are not independent of one another: four of the five studies in the continuous strand also appear in the dichotomous strand, and every bias-adjusted estimate is a function of the same seven effect sizes. They are partly overlapping views of one dataset rather than separate experiments. Taken together, however, they point in one direction. The clinician-graded estimate (1.72), the trim-and-fill estimate (1.83), the precision-effect estimate (1.44), the limit meta-analysis (2.40), the continuous strand entered at its own reported discrimination (2.14) and the race-adjusted estimate from the single low-risk study (1.39) all fall in or near the interval 1.3 to 2.4, while the unstratified pool sits at 3.45. This convergence, together with the area-under-the-curve audit that supports it, is displayed in panels A and B respectively of Figure 7.

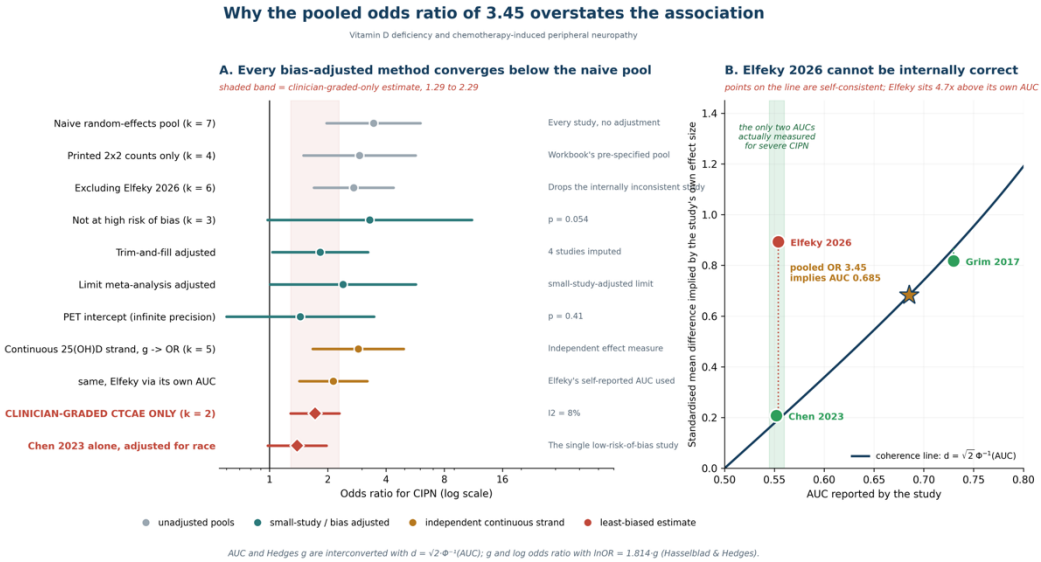

Figure 7. Panel A: every bias-adjusted and independent estimate fell below the unstratified pool and clustered on the clinician-graded band (shaded). Panel B: the internal-consistency check relating each study's reported discrimination to its own reported effect size; points on the line are self-consistent.

The single low-risk study deserves separate mention, because its own analysis shows the association attenuating as confounding is progressively controlled.[38] That sequence is set out in Table 8. The unadjusted odds ratio for grade 3 or worse sensory neuropathy was 1.57 (1.14 to 2.15); adjusted for age and paclitaxel schedule it rose slightly to 1.65 (1.18 to 2.30); and once self-reported race entered the model it fell to 1.39 (0.98 to 1.97) and lost conventional significance. Within either racial group the association was of similar magnitude, 1.40 and 1.42, but no longer statistically significant in either.

Table 8. Attenuation of the association with progressive confounding control in the only study rated at low risk of bias.

Model	Odds ratio for grade ≥3 sensory neuropathy (95% CI)	p	Covariates
Unadjusted, as published	1.57 (1.14 to 2.15)	0.005	—
Recomputed from the printed 2×2 table	1.57 (1.15 to 2.15)	0.005	Value entered into the pooled analysis
Adjusted for age and paclitaxel schedule	1.65 (1.18 to 2.30)	0.003	Age; treatment schedule
Additionally adjusted for self-reported race	1.39 (0.98 to 1.97)	0.066	Age; schedule; race
Within White participants only	1.40 (0.95 to 2.27)	Not significant	Stratified
Within Black participants only	1.42 (0.53 to 4.27)	Not significant	Stratified

All values are as published by the source authors except the second row, which is the crude odds ratio recomputed from that study's printed two-by-two table and is the value carried into the pooled analysis in Table 2 and Figure 3; the two differ only in the third significant figure of the lower limit. CI = confidence interval.

Race is doing a great deal of the work, and the distribution that explains why is given in Table 9. Vitamin D insufficiency was nearly three times as common among Black as among White participants, and Black participants had roughly twice the incidence of severe neuropathy. Two readings remain available and these data cannot separate them: vitamin D insufficiency may mediate part of a racial disparity in neuropathy risk, or race may confound the vitamin D association. That racial disparities in neurotoxicity are real is supported independently, both in solid tumours[13] and in myeloma, where bortezomib-induced neuropathy affected 46% of Black against 34% of non-Black patients.[49] No other study in this synthesis reported race at all.

Table 9. Distribution of vitamin D insufficiency and severe neuropathy by self-reported race in the low-risk study.

Proportion affected (%)	White	Black	Other or unknown
Vitamin D insufficient (≤20 ng/mL)	28.2	77.1	37.6
Grade ≥3 sensory neuropathy	14.3	29.4	23.5

Percentages are as published by the source authors. The odds ratio for vitamin D insufficiency in Black versus White participants was 8.56 (95% CI 5.44 to 13.92).

3.12. Certainty of the evidence and absolute risk

Certainty was rated for three outcomes, domain by domain, as detailed in Table 10. All began at low, as observational studies of an exposure. The unstratified pooled odds ratio was downgraded for risk of bias, for inconsistency and for publication bias, reaching very low. The clinician-graded estimate was downgraded once, for risk of bias, and was rated low — the highest certainty available anywhere in this literature. The continuous strand reached very low. Neither available upgrade was applied. The large-effect upgrade was not defensible because the internal-consistency audit shows the large effect to be an artefact of ascertainment. The dose-response upgrade was not defensible either: the exposure-threshold subgroup test was null, and the only study with a full four-category exposure gradient found the relationship non-monotonic, with the highest neuropathy rate in the group with adequate vitamin D.[46]

Table 10. GRADE certainty of evidence.

Outcome	k	n	Effect	Risk of bias	Inconsistency	Indirectness	Imprecision / Pub. bias	Certainty
Neuropathy, any ascertainment (unstratified pool)	7	2,118	OR 3.45 (1.97–6.03)	Serious	Serious	Not serious	Not serious / Serious	Very low
Neuropathy by clinician-graded NCI-CTCAE	2	1,541	OR 1.72 (1.29–2.29)	Serious	Not serious	Not serious	Not serious / Not serious	Low
Serum 25(OH)D, neuropathy vs none	5	1,876	g 0.58 (0.28–0.88)	Serious	Serious	Not serious	Not serious / Serious	Very low

All three outcomes started at low certainty because every included study was an observational study of an exposure. The Imprecision / Publication bias column gives the imprecision judgement followed by the publication-bias judgement. Neither the large-effect nor the dose-response upgrade was applied, for the reasons given in the text.

The practical consequence of choosing between these estimates is large, and is quantified in Table 11. Against a baseline severe-neuropathy risk of 5.5% observed in vitamin D replete patients, the unstratified pooled odds ratio implies a risk of 16.7% in deficient patients — an absolute increase of 11.2 percentage points and a number needed to harm of 9. The precision-effect-adjusted estimate implies 7.7%, an increase of 2.2 percentage points and a number needed to harm of 45. The number needed to harm therefore differs by a factor of five between the two estimates. That contrast should not be over-read, for two reasons. The intervals overlap substantially, and the precision-effect interval contains the unstratified point estimate, so the two are not statistically distinguishable at this sample size. And the baseline of 5.5% is taken from the replete arm of the study that the internal-consistency audit found contradictory, a study that also supplies 15.9% of the

weight to the odds ratio being applied, so baseline and effect are not independent. The table is therefore offered to show what is at stake in the choice of estimate, not as a set of risk predictions fit for counselling an individual patient.

Table 11. Absolute risk and number needed to harm under alternative estimates.

Outcome	Baseline risk if replete (%)	Estimate applied	Risk if deficient (%)	Absolute difference (pp)	Number needed to harm
Severe (grade ≥3) neuropathy	5.5	Unstratified pooled OR 3.45	16.7 (10.3 to 26.0)	11.2 (4.8 to 20.5)	9 (5 to 21)
Severe (grade ≥3) neuropathy	5.5	Trim-and-fill 1.83	9.6	4.1	24
Severe (grade ≥3) neuropathy	5.5	PET-adjusted 1.44	7.7	2.2	45
Any-grade neuropathy	69.5	Unstratified pooled OR 3.45	88.7 (81.8 to 93.2)	19.2 (12.3 to 23.7)	5 (4 to 8)
Any-grade neuropathy	69.5	PET-adjusted 1.44	76.7	7.2	14

pp = percentage points; PET = precision-effect test. Baseline risks are taken from the two included studies with genuine cohort sampling; the case-enriched cohort cannot supply one. Intervals shown for the unstratified rows are deterministic propagations of the published confidence limits of the pooled odds ratio onto the stated baseline; they do not incorporate uncertainty in the baseline itself, which is substantial. No interval is given for the bias-adjusted rows because those adjustments are exploratory.

4. Discussion

This synthesis assembled every extractable contrast between vitamin D status and chemotherapy-induced peripheral neuropathy. In thirteen of the 14 included studies the direction of effect favoured an association between vitamin D deficiency and neuropathy. The exception must be stated rather than absorbed: one cross-sectional study of 111 patients with myeloma reported explicitly that vitamin D status was unrelated to the occurrence of neuropathy, although deficient patients had more severe neuropathy, and it printed no data that could be pooled.[42] The unstratified pooled odds ratio was 3.45. The more important finding, however, is that this number is not the answer. How neuropathy was ascertained explained 93.5% of the variation between studies, and the two ascertainment routes gave estimates differing threefold: 5.27 where patients reported their own symptoms, 1.72 where clinicians assigned a Common Terminology Criteria grade. Within each route the studies were homogeneous, with I^2 of zero and 8%. A literature that looks chaotic turns out to be two internally consistent literatures that have been read as one.

4.1. Interpretation

Three independent lines of evidence indicate that the clinician-graded estimate, not the unstratified pool, is the defensible one. The first is small-study-effect adjustment: trim-and-fill returned 1.83, limit meta-analysis 2.40 and the precision-effect test 1.44. The second is the internal-consistency audit. An odds ratio of 3.45 corresponds to an area under the receiver operating characteristic curve of 0.685, yet the only two studies that measured how well 25-hydroxyvitamin D discriminates severe neuropathy obtained 0.552 and 0.554. A biomarker that discriminates that weakly cannot generate a threefold odds ratio. The third is the continuous strand, which used a different effect measure on partly different data and returned an equivalent odds ratio of 2.87, falling to 2.14 once the one internally inconsistent study was entered at its own reported discrimination. Three methods, three different assumptions, one destination.

Why should ascertainment matter so much? The answer is concrete rather than abstract, and it is worth setting out in the terms a clinician uses. Under the Common Terminology Criteria for Adverse Events, grade 1 sensory neuropathy means the patient is asymptomatic or has paraesthesiae that do not interfere with function; grade 2 requires limitation of instrumental activities of daily living, such as shopping, cooking or handling money; and grade 3 requires limitation of self-care, such as bathing or dressing. The grade is assigned by an oncologist in a busy clinic, usually on the strength of an open question rather than a structured examination of vibration sense, pinprick and ankle reflexes. Grade 1 therefore absorbs an extremely wide band of genuine sensory disturbance. A patient who can no longer feel the pedals of a motorcycle, who fumbles buttons and coins, and who has lost vibration sense at the ankles, but who still bathes and dresses unaided, will be recorded as grade 1 or not recorded at all. The same patient completing a symptom questionnaire will report numbness, tingling and difficulty with fine movement, and will be counted as a case. That single gap between what is elicited and what is experienced is the concrete reason clinician grading returned 1.72 where patient report returned 5.27. The likely mechanism is therefore differential detection. Clinician grading of neurotoxicity systematically under-records what patients experience, and it does so unevenly. In the phase III PANTHER trial, weighted kappa between clinician and patient ratings ranged from 0.07 to 0.34, with discrepancy rates reaching 54%.[28] In phase I trials, nineteen symptomatic adverse events were clinician-reported at 1% or less against patient-reported rates of 10% or more, with some items showing a fiftyfold gap.[29] In routine outpatient practice, agreement for peripheral neuropathy specifically was fair to moderate at best.[30] Patient-reported measures also outperform clinician and neurophysiological tools on convergent validity and responsiveness.[32] A patient-reported instrument therefore detects more of the mild and moderate neuropathy that clinician grading misses. If vitamin D deficient patients are more likely to volunteer such symptoms, or if their milder neuropathy is precisely the part clinicians overlook, the association will look larger through the patient-reported lens. It is also worth recording that these two routes do not measure the same construct: an analysis of 372 patients with established neuropathy found substantial overlap in patient-reported scores across different

clinician-assigned grades.[50] A qualification belongs here that cuts against the tidiness of the finding. The patient-reported stratum is statistically homogeneous but clinically it is not. It contains the Michigan Neuropathy Screening Instrument, whose original form combines a self-administered questionnaire with a physical examination of foot inspection, vibration and ankle reflexes; the Douleur Neuropathique en 4 questions, which identifies neuropathic pain and will score negative in a patient with painless numbness and impaired vibration sense, so that it misses precisely the large-fibre loss that dominates the taxane phenotype; the twenty-item chemotherapy-induced neuropathy module, with sensory, motor and autonomic subscales; and two unnamed questionnaires. These instruments do not interrogate the same fibre populations or the same construct. Grouping them and calling the moderator ascertainment therefore conflates who does the reporting, what is measured and which fibres are tested. That five clinically disparate instruments nonetheless produced statistically homogeneous estimates is itself interesting, and may indicate that the dominant signal is the act of asking the patient rather than the particular question asked. It may equally indicate that five small studies cannot be shown to disagree. The alternative explanation for the whole moderator is that patient-reported instruments are the more valid measure and clinician grading attenuates a real association towards the null.

If that alternative is correct, then the price of preferring the clinician-graded estimate, as this review does, is the adoption of the less sensitive outcome measure. The authors accept that trade-off deliberately, because the clinician-graded estimate is the one corroborated by every bias-adjusted method, by the discrimination the primary studies actually measured, and by the only low-risk-of-bias study in the set. But the true clinically meaningful association may well lie between 1.72 and 5.27 rather than at either end, and nothing in these data can locate it more precisely.

Neither reading can be settled by the present data, because the two clinician-graded studies were also the two largest, so that adjusting for sample size attenuated the moderator to borderline significance. Both explanations, however, carry the same practical implication: the unstratified estimate of 3.45 is inflated, and the large clinician-graded studies give the more trustworthy figure.

The single low-risk study reinforces this reading from a different direction. Its association fell from 1.65 to 1.39, and lost conventional significance, once self-reported race entered the model.[38] Because 77.1% of Black participants were vitamin D insufficient against 28.2% of White participants, and because racial disparities in neurotoxicity are independently documented in both solid tumours[13] and myeloma,[49] vitamin D status and ancestry are deeply entangled in this literature. Whether vitamin D mediates part of that disparity or merely marks it is a question no included study was designed to answer.

4.2. Comparison with other syntheses

One previous meta-analysis has reported a pooled estimate for this exposure, as one line among sixteen candidate influencing factors for chemotherapy-induced peripheral neuropathy; it pooled two studies and obtained an odds ratio of 5.63 (2.64 to 11.99).[26] The present synthesis pools seven studies and obtains 3.45 unstratified and 1.72 in the clinician-graded stratum. The difference is instructive rather than contradictory: a two-study estimate cannot be stratified, cannot be tested for small-study effects and cannot produce a prediction interval, and the direction of the discrepancy is exactly what the ascertainment moderator predicts. The only dedicated review of this question is a scoping review that mapped eleven observational studies narratively and, by design, produced no pooled estimate, no heterogeneity statistic and no assessment of bias.[25] Every one of its eleven studies is contained within the present included set, which additionally holds three that it does not.

The nearest quantitative analogue lies outside oncology. In painful diabetic neuropathy, a meta-analysis of four randomised trials found a standardised mean difference of −0.85 (−1.07 to −0.62) favouring vitamin D.[27] That estimate comes from randomised evidence and is therefore not directly comparable with the observational association reported here, but it makes the biological premise credible: the same vitamin appears to matter for a different peripheral neuropathy, in trials rather than cohorts. Supporting observational work in diabetes is consistent, whether neuropathy is defined by nerve conduction study,[15] by electromyography and skin conductance,[16] by intraepidermal nerve fibre density[18] or by vitamin D receptor expression in peripheral blood mononuclear cells.[19] The observation that the relationship in diabetes is non-linear, steepening below roughly 26 ng/mL,[17] may also explain why the threshold subgroup analysis reported here was null: thresholds ranging from 12 to 30 ng/mL will not produce an orderly gradient if the true relationship has a knee.

The randomised evidence on vitamin D and pain outside neuropathy is, by contrast, largely negative and should temper expectations. A 12-week trial in fibromyalgia found no benefit despite confirmed biochemical repletion.[51] The VITAL ancillary study of 19,611 participants found no reduction in pain prevalence or severity over a median 5.3 years.[52] The D-Health trial of 21,315 older adults found an adjusted mean pain difference of 0.02 (−0.20 to 0.25).[53] A positive signal does exist in diabetic neuropathy specifically, where an Indonesian randomised trial of 5,000 IU daily added to standard treatment produced a greater reduction in pain than standard treatment alone.[54] The pattern that emerges is that vitamin D repletion may help neuropathic pain in deficient patients while doing nothing for unselected pain in replete populations — which is an argument for testing it in deficient patients receiving neurotoxic chemotherapy, not for assuming it will work.

4.3. Heterogeneity

Heterogeneity in the unstratified pool was substantial (I^2 74.6%, τ^2 0.367) and the prediction interval ran from 0.67 to 17.76, crossing the null. Rather than describing this and moving on, the analysis attempted to account for it, and largely succeeded. Ascertainment method reduced residual I^2 to 13.2% and residual τ^2 from 0.367 to 0.022. Nothing else came close: assay platform explained 38.1%, the logarithm of sample size 41.2%, and risk of bias, outcome construct, publication year and tumour restriction explained none at all. It is worth stating what the null moderators mean. Tumour type was null (p = 0.848), so the myeloma studies did not behave differently from the solid-tumour studies, though with one myeloma study in the pool this is a weak test and the confounding it should have detected is real. Myeloma causes neuropathy in its own right: in 155 newly diagnosed patients, pre-treatment disease-related neuropathy was age-related and predicted both more severe bortezomib-induced neuropathy and worse survival,[55] while bortezomib itself raised treatment-emergent neuropathy from 9% to 24% in a matched claims cohort.[56] Disease-related and treatment-related neuropathy cannot be separated in the myeloma studies included here, none of which excluded baseline neuropathy. The point deserves more space than a subgroup p value affords, because neuropathy in myeloma is not one disease. Light-chain amyloid deposition produces a painful small-fibre and autonomic neuropathy, often with carpal tunnel syndrome and orthostatic hypotension. Paraproteinaemic mechanisms can produce a demyelinating picture. Osteosclerotic myeloma may present as the polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes syndrome, which is a demyelinating polyradiculoneuropathy. Cryoglobulinaemia, radiculopathy from vertebral collapse or plasmacytoma, hypercalcaemia and renal failure each contribute further mechanisms, and thalidomide as well as bortezomib adds a treatment-related axonal component. Vitamin D deficiency in myeloma is itself entangled with renal impairment, skeletal disease and corticosteroid exposure. Pooling a myeloma cohort with a taxane-treated breast cohort under one outcome label therefore combines at least two different diseases of nerve, and the null tumour-type moderator should not be taken as evidence that this does not matter. Provenance of the two-by-two table was null (p = 0.509), so the reconstructed contrasts did not drive the result; the restricted pool of printed counts alone still gave 2.92. Exposure threshold was null (p = 0.405), which given eleven studies that never stated an assay and two that never stated a threshold at all should be read as an absence of information rather than an absence of effect.

4.4. Limitations

This review has several limitations, and they are more consequential than usual because the evidence base is small and unevenly reported. Only seven studies could be pooled, and this ceiling is structural: two databases, deduplicated citation chasing in both directions across eight seed papers, and item-by-item resolution of the only dedicated review of this question all failed to add an eligible primary study. Consequently every small-study-effect analysis reported here falls below the ten-study threshold at which such tests have useful power, and is exploratory; the permutation test for the principal moderator returned exactly its own arithmetic floor of 0.0476 and therefore carries no resolution beyond that. The association did not survive restriction to the better-conducted studies: eleven of 14 studies were at high risk of bias on ROBINS-E, driven by exposure measurement (high in 64%) and confounding (high in 57%), and restriction to the three studies not at high risk gave 3.30 (0.98 to 11.11) with p = 0.054, while the single low-risk study lost significance once race was adjusted for. The exposure is poorly characterised across most of the literature: only one study used the reference assay, eleven never stated an assay platform, two never printed units, a threshold or a concentration anywhere, and two described measurement in terms that are not physically possible for 25-hydroxyvitamin D or that contradict their own methods sections, so no threshold recommendation can responsibly be drawn. One influential study is internally inconsistent, its Cook distance of 0.69 moving the pooled estimate from 3.45 to 2.72 on omission and its reported area under the curve being incompatible by a factor of 4.7 with its own reported group means.[35] Competing causes of neuropathy were largely uncontrolled — the largest contributing study collected neither diabetes status nor pre-existing neuropathy[38] — and diabetes, obesity, older age, low haemoglobin and pharmacogenomic variation are all established determinants of neurotoxicity[10–12,14] that also cause vitamin D deficiency, so residual confounding is likely to inflate the association. The one clearly null result could not be pooled because it printed no extractable data, biasing the pooled estimate upward invisibly.[42] The two reconstructed contrasts carry specific quantifiable biases: one was back-solved from a data-derived cut-off,[39] the other from a published odds ratio for neuropathy-induced treatment disruption, a clinician-initiated dose modification arguably belonging in the clinician-ascertained stratum,[44] and the pre-specified restricted pool of printed counts alone, which excludes both, gave 2.92 (1.50 to 5.68). Reverse causation cannot be excluded in any included study, since patients who are unwell, immobile, indoors or cachectic have lower 25-hydroxyvitamin D and none of the studies measured performance status, diet or sun exposure. The patient-reported stratum is clinically heterogeneous even though statistically homogeneous, and ascertainment, sample size, data provenance and assay platform are mutually confounded, so the moderator identifies a partition of the literature rather than a mechanism. Finally, the review process was not duplicated — screening, extraction and appraisal were done by a single reviewer, the two reconstructions were not independently checked, and language bias cannot be excluded — several expected analyses were

deliberately not run and no substitute values were generated, and causal inference is not available because every included study was observational, the one interventional study single-arm and uncontrolled,[47] and the review was not prospectively registered.

4.5. Implications for neurological practice

Four implications follow, and they are deliberately modest. First, for the clinician, measuring 25-hydroxyvitamin D before neurotoxic chemotherapy is a defensible low-cost action, but it should be framed as risk stratification rather than prevention. Even on the clinician-graded estimate the association is real, and the exposure is extraordinarily common in the populations these authors serve — 73% deficient or insufficient among Indonesian women in an equatorial province,[20] every patient deficient in one Indonesian breast cancer cohort,[21] 93.9% with low vitamin D in urban Sri Lanka,[22] and half of Thai patients with advanced colorectal cancer.[24] A patient identified as deficient can reasonably be repleted on general grounds, monitored more closely for early neurotoxicity, and counselled that the evidence that repletion prevents neuropathy does not yet exist. Second, the absolute numbers should be quoted honestly. Against a 5.5% baseline, the number needed to harm ranges from 9 to 45 depending on which estimate is believed; a clinician who quotes only the first figure is overstating what is known by a factor of five.

Third, the practical questions a district-hospital neurologist will ask deserve direct answers rather than a recommendation in principle. A serum 25-hydroxyvitamin D assay is not a bedside test in most Indonesian district hospitals; it is usually referred to a regional or private laboratory, with a turnaround of days, and is not universally covered by national health insurance, so the cost may fall to the patient. The platforms available in such laboratories are automated immunoassays, and this review has just identified assay quality as the single weakest risk-of-bias domain in the underlying literature. That is an uncomfortable tension and it should be stated rather than glossed: the test a clinician can actually obtain is the test this synthesis is least able to vouch for. Where repletion is undertaken it should follow standard endocrine practice for nutritional deficiency rather than any regimen derived from this review, since no trial in oncology supports a specific dose, and serum calcium warrants attention at high cumulative doses. What can be recommended without reference to vitamin D at all is better neurological baseline documentation: vibration threshold at the hallux, ankle reflexes and a brief pinprick level recorded before the first cycle, and a structured symptom enquiry at each subsequent cycle rather than an open question. That single change addresses the detection problem this review has identified, costs nothing, and would improve care whatever the vitamin D result.

A harder question follows from the authors' own data, and it argues against testing. If, as reported in an Indonesian breast cancer cohort, essentially every patient assessed was vitamin D deficient with a median concentration of 8.94 ng/mL,[21] then measurement has almost no discriminative value in that population: a test that returns the same answer for everyone stratifies nobody. Where local prevalence approaches unity, empirical repletion on general nutritional grounds is the more logical policy, and the assay budget is better spent elsewhere. Where prevalence is intermediate, testing regains its purpose. Clinicians should therefore be guided by local prevalence data rather than by a universal recommendation to test, and generating those local data is itself a worthwhile piece of work.

Fourth, and most usefully, this review yields a design instruction for the next study. If a single measurement choice explains 93.5% of the disagreement in a literature, then trials and cohorts in this field should collect both a clinician-graded and a patient-reported neuropathy outcome and report the association against each. That is a cheap addition and it would settle in one study a question that seven could not. The trial the field actually needs is a randomised comparison of vitamin D repletion against usual care in patients who are deficient at baseline and about to start a taxane or a proteasome inhibitor, powered on a clinician-graded grade 2 or worse endpoint with a patient-reported instrument alongside, and stratified by ancestry. It should measure 25-hydroxyvitamin D by mass spectrometry, state its threshold, exclude pre-existing neuropathy and record diabetes — four things most of the existing literature did not do. Such a trial is feasible: neuromuscular training and hand cooling have both already been tested against neuropathy endpoints in randomised designs,[7,8] and vitamin D repletion is cheaper and simpler than either. Until it is done, vitamin D deficiency should be regarded as a marker of elevated risk in patients receiving neurotoxic chemotherapy, and not as a treatable cause of neuropathy.

5. Conclusion

Vitamin D deficiency or insufficiency was associated with chemotherapy-induced peripheral neuropathy in adults receiving neurotoxic chemotherapy. The direction of effect favoured an association in 13 of the 14 included studies, the exception being a myeloma cohort that found no relationship with neuropathy occurrence and could not be pooled, and the unstratified random-effects pooled odds ratio across the seven poolable contrasts was 3.45 (95% confidence interval 1.97 to 6.03). That figure, however, should not be carried into practice. The method by which neuropathy was ascertained explained 93.5% of the between-study variance and split the literature into two internally homogeneous halves: studies using patient-reported instruments gave 5.27 (3.41 to 8.13) while studies using clinician-graded Common Terminology Criteria gave 1.72 (1.29 to 2.29). Small-study-effect adjustment, an internal-consistency audit against each study's own reported discrimination, and an independent analysis of the serum 25-hydroxyvitamin D concentration all converged on the lower figure.

The defensible conclusion is therefore that vitamin D deficiency is associated with roughly a 1.7- to 2.4-fold increase in the odds of chemotherapy-induced peripheral neuropathy, not the threefold increase the unstratified analysis suggests. Certainty was very low for the unstratified estimate and low for the clinician-graded one, the latter being the highest certainty this literature currently supports. The three studies not at high risk of bias did not agree with one another and their pooled interval included the null, the single low-risk study lost statistical significance once race was adjusted for, and no threshold for intervention can be recommended, because thresholds across studies ranged from 12 to 30 ng/mL, the threshold subgroup test was null, and the only study with a full exposure gradient found it non-monotonic.

For neurological practice, measuring 25-hydroxyvitamin D before neurotoxic chemotherapy is a reasonable and inexpensive means of identifying patients at higher risk, particularly in equatorial populations where deficiency is common despite abundant sunlight. It is not, on present evidence, a preventive treatment. The most useful product of this synthesis may be methodological: a single measurement choice accounted for almost all of the disagreement in this field, and future studies should report their association against both a clinician-graded and a patient-reported neuropathy outcome so that this ambiguity is not perpetuated.

6. Declarations

6.1. Ethics approval and consent to participate

This study was a synthesis of previously published, de-identified aggregate data. No new human or animal data were collected and no individual participant data were accessed, so institutional ethical approval and informed consent were not required. Ethical approval for each included study was the responsibility of its original investigators. The review was not prospectively registered and no protocol was lodged in a public repository. An internal analysis plan was written before the pooled analyses were run, and the ascertainment moderator was named in that plan; because the plan was not registered, readers should treat that pre-specification as an assertion by the authors rather than as an independently verifiable fact, and should weight it accordingly. Retrospective registration and deposition of the analysis code are intended.

6.2. Consent for publication

Not applicable. No identifiable individual patient data, images or clinical details are presented.

6.3. Availability of data and materials

The extraction workbook, the analysis dataset, the risk-of-bias assessments and the analysis code are available from the corresponding author on reasonable request. Because two of the seven pooled contrasts were reconstructed from published statistics rather than printed by their authors, the arithmetic of those reconstructions is included in that material so that any reader may check it independently.

6.4. Competing interests

The authors declare that they have no competing interests.

6.5. Funding

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6.6. Author contributions

C conceived the review question, designed the search, screened records, extracted the data, appraised risk of bias and drafted the manuscript. IASW supervised the project, adjudicated the eligibility and reconstruction decisions, and critically revised the manuscript for important intellectual content. KT contributed to the clinical interpretation and to the revision of the manuscript. All authors read and approved the final version and agree to be accountable for all aspects of the work.

6.7. Use of generative artificial intelligence

Generative artificial intelligence was not used to generate data, statistical results, interpretations or conclusions. All analytical and interpretive work, and the final wording, were performed and verified by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

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